Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YAWEN L. CHIANG and ESTHER H. CHANG

Appeal No. 1999-1330
Application No. 08/527,373

ON BRIEF

Before WINTERS, ROBINSON, and ADAMS, Administrative Patent Judges.

ROBINSON, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 - 11, which are all of the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and reads as follows:

1. A process for improving the treatment of a tumor by radiation therapy comprising:

treating a tumor by radiation therapy wherein cells of said tumor have been transduced with a polynucleotide encoding wild type p53.

The references relied on by the examiner are:

Nabeya et al. (Nabeya), "The Mutational Status of p53 Protein in Gastric Cancer Cell Lines Predicts Sensitivity to Chemotherapeutic Agents," Proceedings of the American Association for Cancer Research, Vol. 35, (abstract 3591), p. 602 (March 1994)

Liu et al. (Liu), "Growth Suppression of Human Head and Neck Cancer Cells by the Introduction of a Wild-Type p53 Gene via a Recombinant Adenovirus," Cancer Research, Vol. 54, pp. 3662-3667 (July 1994)

Wills et al. (Wills), "Development and Characterization of Recombinant Adenoviruses Encoding Human p53 for Gene Therapy of Cancer," Human Gene Therapy, Vol. 5, pp. 1079-1088 (September 1994)

Orkin et al. (Orkin)[1], "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," NIH Report and Recommendation, (December 1995)

The reference relied on by appellants is listed below:

Jung et al. (Jung), "Mutations in the p53 Gene in Radiation-sensitive and -resistant Human Squamous Carcinoma Cells," Cancer Research, Vol. 52, pp. 6390-6393 (1992)

Grounds of Rejection

Claims 1 - 11 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure for the breadth of the claimed invention. As evidence, the examiner relies on Orkin.

Claims 1 - 11 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies upon Wills, Liu, and Nabeya.

[1] We note that this reference was published subsequent to the filing date of the application.

We reverse the rejection under 35 U.S.C. § 112, first paragraph, and affirm the rejection of claims 1 - 11 under 35 U.S.C. § 103 for reasons set forth herein.

Discussion

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer of February 17, 1998 (Paper No. 13) for the examiner's reasoning in support of the rejections and to the appellants' Appeal Brief filed November 26, 1997 (Paper No. 12) for the appellants' arguments thereagainst.

Grouping of the claims

The appellants' Appeal Brief at page 4, states that the claims do not stand or fall together. The examiner at page 3 of the Examiner's Answer, urges that the claims do stand and fall together because appellants fail to explain why each claim is separately patentable. Appellants have not further disputed the examiner's position and since the brief fails to separately address the patentability of the claims on appeal, the claims are considered to stand and fall together. We have limited our consideration of the issues raised by this appeal as they apply to claim 1 as representative of claims 1 - 11. (37 CFR 1.192 (c)(7) (1997)).

Claim Interpretation

Claim 1 is directed to a process of improving the treatment of a tumor using radiation therapy comprising treating the tumor with radiation therapy wherein the cells of the tumor have been transduced with a polynucleotide encoding wild-type p53. Appellants indicate that transduction of radiation resistant tumor cells in this manner can reverse the radiation resistance of such tumor cells. (Specification, page 6). The specification explains that "'treating a tumor' as used herein means that one provides for the inhibition, prevention, or destruction of the growth of the tumor cells." (Id.). The wild-type p53 protein is a natural occurring protein associated with cell growth regulation which has been found to function as an oncogene in its mutated form and a tumor suppressor gene in its wild-type form. (Jung, page 6390, column 1, third paragraph.)

The rejection under 35 U.S.C. § 112, first paragraph

Claims 1 - 11 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on a disclosure which "fails to provide an enabling disclosure for any 'improved' embodiment of cancer treatment." (Answer, page 9). While acknowledging that the specification "enables the reduction of cancer cell lines implanted subcutaneously in **nude** mice which have been transduced to express wild-type p53 protein via adenoviral vectors and then irradiated," the examiner urges that "the specification fails to enable any treatment methodology for naturally occurring cancers in humans." (Answer, page 9). In explaining the basis of this rejection, the examiner has focused on that aspect of

the claimed method which requires that the tumor cells have been transduced with a polynucleotide encoding wild-type p53.

The examiner relies on Orkin as indicating the "importance of relevant animal models" and as stating "that 'many mouse models often do not faithfully mimic the relevant human conditions.'" (Answer, page 10). The examiner, additionally, notes the statements of Orkin which are urged to establish that "the relevance of results from animal models with respect to correlation of human treatment are even more unpredictable 'with respect to the efficiency of gene delivery and the host response to viral vectors.'" (Answer, page 10).

The examiner, further, urges that (Answer, paragraph bridging pages 10-11):

> [a]ppellants' nude mouse model cancer system does not measure or take into account the immune response that would be generated in a human patient, for example, against the adenoviral vector or any other viral vector embodied in the claimed invention. Thus, a nude mouse model, where the animal lacks T-cells to mount an effective immune response, is not a representative animal model for evaluating naturally occurring cancer regression in an immunocompetent animal such as a human due to the unpredictability of the immune reaction to the viral vector, the unpredictability of generating a threshold protein expression level in transduced cells, and the unknown effect of the experimental system on naturally occurring cancers which evaded immune detection in vivo.

The examiner concludes that (Answer, page 11):

> in view of the quantity of experimentation necessary to determine the treatment parameters for naturally occurring

> tumors, the lack of direction or guidance provided by the specification, the absence of working examples for in vivo cancer therapy, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to in vivo cell transformation and gene therapy, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

In response to the examiner's position, the appellants urge that Wills and Liu, relied on by the examiner in the prior art rejection, also employ a nude mouse model and that "the nude mouse model . . . is an acceptable animal model for the treatment of tumors." (Brief, page 8). In response to the examiner's criticism of the direction and guidance provided by the specification, the appellants urges that the specification provides (Brief, page 9):

> dosage ranges for adenoviral vectors at Pages 11 and 17 of the specification, and dosage ranges for retrovial vectors at Page 15. Examples of methods of administration of the viral vectors, such as, for example, direct administration to the tumor, intravenous, intraarterial, or intraperitonal [sic] administration, are provided at Pages 10 and 11. [Thus] [o]ne skilled in the art would understand readily that the exact dosage of viral vector to be administered and the method of administration are dependent upon a variety of factors, including the age, weight, and sex of the patient, the type of tumor being treated, and the severity thereof.

Appellants, additionally, note that the specification provides two working examples, Examples 3 and 4, in which squamous cell carcinoma was treated with the claimed combination of radiation and an adenoviral vector including the wild-type p53 gene in an animal model.

Therefore, the issue presented by this rejection is whether applicants' disclosure would have enabled one skilled in the art to make and use the claimed invention throughout its scope without undue experimentation. In such cases, the Patent and

Trademark Office (PTO) bears the initial burden of providing reasons for doubting the objective truth of the statements made by applicants as to the scope of enablement. Only when the PTO meets this burden, does the burden shift to applicants to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Factors appropriate for determining whether undue experimentation is required to practice the claimed invention throughout its full scope are listed in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

On the record before us, we find that the examiner's statements and evidence in support of this rejection, when weighed against the appellants' disclosure in support of the claimed invention and arguments, fail to provide adequate evidence or reasons why one skilled in the art would doubt the statements relating to the manner of improving the treatment of a tumor by treating the tumor with radiation therapy wherein the cells of the tumor have been transduced with a polynucleotide encoding wild-type p53. The general conclusions relating to the Wands factors are not supported by facts or evidence which would provide a reasonable basis for concluding that the present disclosure does not enable the full scope of the claimed subject matter. We point out that the level of unpredictability in the art is merely one of the factors to be considered in determining whether the disclosure provided by applicants in support of a claimed invention is sufficient to permit those skilled in the art to which the invention relates to practice the invention without undue experimentation. That some experimentation may be necessary, does not equate to undue experimentation. Further, it is well settled that

patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976).

The examiner has premised this rejection on two propositions. The first is that the nude mouse is not a predictable model for the treatment of tumors in humans. Yet, as pointed out by the appellants, both Wills and Liu make use of this same model in their studies. To the extent that it can be urged that these publications are representative of those studying this type of treatment, they provide a strong indication that the nude mouse is the accepted model in studies of this type of cancer or tumor treatment and are considered reasonably predictive of future use in other animals such as humans by those skilled in this art. The second proposition appears to be that the specification lacks sufficient guidance as to the mode of administration, appropriate viral vector to use and the unpredictability of the vector targeting the appropriate tumor cells in vivo in a human patient. (Answer, pages 11-12). The examiner does not explain why the disclosure provided by the specification relating to the administration of vectors and cells, noted by appellants supra, does not provide sufficient guidance for practicing the invention without undue experimentation. In addition, we note the discussion in Wills at page 1086, column 2, starting with the first full paragraph which explicitly addresses the use of gene therapy in humans. This discussion reasonably suggests that:

> Adenoviruses have never been shown to induce tumors in humans and have been safely used as live vaccines. . . . Others have shown that adenovirus-medicated gene delivery has a strong potential for gene therapy . . . Although other alternatives for gene delivery . . . are also currently being explored, none as yet appear as effective as adenovirus-mediated gene delivery.
>
> Here, we have shown that recombinant adenovirus expressing wild-type p53 can efficiently inhibit DNA synthesis and suppress the growth of a broad range of human tumor cell types, . . . the data presented here strongly support the concept of adenovirus-mediated p53 gene therapy of p53-deficient tumors in humans.

This portion of Wills would reasonably suggest that one skilled in this art, reading the disclosure presented in support of the claimed invention, would have accepted the statements concerning how to practice the invention in the manner described by appellants.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). On balance, we find the appellants' arguments and evidence in favor of patentability persuasive when weighed against the examiner's evidence and arguments provided in support of the rejection. Therefore, the rejection of claims 1 - 11 under 35 U.S.C. § 112, first paragraph, is reversed.

The rejection under 35 U.S.C. § 103

Claims 1 - 11 stand rejected under 35 U.S.C. § 103 as being obvious over Wills in view of Liu and Nabeya. In so doing, the examiner has interpreted representative

claim 1, as encompassing a method of treating a tumor in nude mice, including the nude mouse used by both Wills and Liu.

The examiner relies on Wills as disclosing (Answer, page 5):

> inhibition of tumor proliferation and tumorigenicity following a single injection of recombinant adenoviral vectors encoding wild-type p53 protein into carcinoma cell lines grown . . . into established tumor in vivo in a nude mouse. . . . Additionally, at page 1086, column 2, Wills et al[.] suggests that the ability to express wild-type p53 in cancer cells may increase the tumor cells susceptibility to radiation therapy or chemotherapy.

The examiner relies on Liu as teaching (Answer, page 6):

> the growth suppression of squamous cell carcinoma of human head and neck cancer (SCCHN) established in vivo in nude mice following the administration of adenoviral vectors encoding wild-type p53.

The examiner relies on Nabeya as having determined that the level of wild-type p53 expression was increased in gastric cancer cells following treatment with chemotherapeutic agents and for the conclusion that "the increased level of p53 protein by the cancer cells renders these cells more susceptible to chemotherapeutic agents." (Id.)

The examiner concludes that (Answer, page 7):

> it would have been obvious to one of ordinary skill in the art to combine the teachings of Wills et al., Liu et al., and Nabeya et al. in order to treat tumor burden in vivo via the administration of adenoviral vectors encoding p53 in combination with radiation therapy with a reasonable

> expectation of success. One of ordinary skill in the art would have been motivated to combine these teachings given that all three references are related to the regression of carcinoma using wild-type p53.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On the record before us, we find no error in the examiner's determination that the combined disclosures of Wills, Liu, and Nabeya are sufficient to establish a prima facie case of obviousness within the meaning of 35 U.S.C. § 103 as to the subject matter of representative claim 1.

Thus, the examiner has provided evidence which would reasonably establish that the claimed subject matter would have been prima facie obvious within the meaning of 35 U.S.C. § 103 at the time of the invention. Where, as here, a prima facie case of obviousness has been established, the burden of going forward shifts to the appellants. In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

Appellants, initially, argue that (Brief, page 6):

> Wills only discloses the administration of adenoviral vectors including a p53 gene to nude mice having an established tumor. Wills provides no examples in which tumors are treated with a combination of p53 gene therapy and radiation. Applicants are aware of the citation by the Examiner of the passage at Page 1086, column 2, of Wills

> which states that tumors supplied with functional p53 may become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy. This passage, however, is mere speculation on the part of Wills that one may treat tumors with a combination of p53 gene therapy and radiation.

However, as pointed out by the examiner (Answer, page 15), to the extent that the suggestion of Wills may be speculation, this statement, when combined with the teaching of Nabeya which teaches that an advantage is obtained when the amount of wild-type p53 is increased in cells subject to chemotherapy, raises the expectation that similar advantage would be obtained by combining the gene therapy relating to wild-type p53 with radiation therapy in the treatment of tumors and tumor cells. As pointed out by the examiner this interpretation is bolstered by the description in Wills at page 1086, paragraph bridging cols. 1 and 2, which provides:

> Wild-type p53 has recently been identified as a necessary component for apoptosis induced by irradiation or treatment with some chemotherapeutic agents. Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may have become so due in part to the lack of wild-type p53. By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy. (Citations omitted).

Nabeya confirms the Wills proposition, at least with regard to chemotherapy, and would reasonably suggest the likelihood of similar results if increased levels of cellular wild-type p53 were combined with radiation therapy.

Appellants, further, rely on Jung as establishing that there is no correlation between mutations in the p53 gene and radiation sensitivity or radiation resistance.

(Brief, paragraph bridging pages 6-7). However, as pointed out by the examiner, this article was published two years prior to the publication date of Wills (Answer, page 16). Further to the extent that Jung would have suggested that there was no relationship between the amount of wild-type p53 present in a tumor cell and the cell's susceptibility to treatment with either chemotherapy or radiation, both later published articles of Wills and Nabeya reasonably establish the significance of the presence in a tumor cell of wild-type p53 and the susceptibility of that cell to damage due to chemotherapeutic agents and radiation therapy which is not rebutted by subsequent evidence. Further, we read Jung somewhat differently from appellants. We note, for example, the statement (page 6393, column 1, first full paragraph):

> Recently, Kastan et al. (20) have reported that p53 may play a role in cellular response to gamma-radiation damage. Cells that either lack p53 gene expression or overexpress a mutant p53 do not exhibit a G_1 arrest, but G_2 arrest is unaffected. This suggests that wild-type p53 may be involved in DNA synthesis inhibition following radiation damage of DNA and provide a cell cycle "check point" (21). The fidelity of DNA repair during cell cycle arrest may play a role in the capacity of cells to tolerate radiation injury and therefore have an impact on radiation sensitivity. In this study, we investigated alterations of the p53 gene and correlated these to the response of cells to ionizing radiation by analyzing the p53 gene in six human SCC cell lines characterized as RS or RR.

The conclusion reached by Jung and quoted by appellants (Brief, page 7) that "Jung indicates clearly that there is no correlation between mutations in the p53 gene and radiation sensitivity or radiation resistance," does not appear to have resulted from

studies which would reflect an increase in the amount of wild-type p53 in cells to be subjected to radiation, but reflect data in which the presence of altered p53 is present in cells. Thus, this information does not reasonably appear to be as relevant to the claimed subject matter as the disclosures of Wills, Liu, and Nabeya.

To the extent that appellants urge that "[t]he cited prior art provides no reasonable expectation that the claimed method would be successful in improving the treatment of tumors, and therefore the content of the cited prior art provides an insufficient basis for the formation of a rejection under 35 U.S.C. § 103," (Brief, page 7) we would remind appellants that absolute predictability is not required, but only a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Here, the examiner has established, through the teachings of the references relied on, that one of ordinary skill would have been led to combine the treatment of tumors, particularly in nude mice, using the transformation of tumor cells with a polynucleotide which would encode wild-type p53 and use that treatment in combination with the conventional radiation treatment, with at least a reasonable expectation of obtaining improved results in the treatment or the tumor. It also must be remembered, to the extent that the appellants have addressed the teachings of the individual reference, that the test is not what the individual references, standing alone, would have suggested to a person having ordinary skill in the art. "Rather, the test is what the combined teachings of the references would have

suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981).

When considered anew, we find, on balance, that the evidence and arguments presented by the appellants, taken as a whole, fail to outweigh the evidence of obviousness provided by the examiner. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988), cert. denied, 493 U.S. 814 (1989); and In re Beattie, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1043 (Fed. Cir. 1992). Thus, the examiner has established a prima facie case of obviousness within the meaning of 35 U.S.C. § 103, which appellants have not overcome either by arguments or convincing evidence. Therefore, we affirm the rejection of representative claim 1, as well as claims 2 -11 under 35 U.S.C. § 103.

Summary

The rejection of claims 1 - 11 under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claimed subject matter is reversed. The rejection of claims 1 - 11 under 35 U.S.C. § 103 as unpatentable over Wills, Liu, and Nabeya is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

SHERMAN D. WINTERS Administrative Patent Judge	)
DOUGLAS W. ROBINSON Administrative Patent Judge	) BOARD OF PATENT)) APPEALS AND)) INTERFERENCES
DONALD E. ADAMS Administrative Patent Judge	)

RAYMOND J. LILLIE
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